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# Varying Vaccination Rates Among Patients Seeking Care for Acute Respiratory Illness: A Systematic Review and Meta-analysis

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**Background.** Complications following influenza infection are a major cause of morbidity and mortality, and the Centers for Disease Control Advisory Committee on Immunization Practices recommends universal annual vaccination. However, vaccination rates have remained significantly lower than the Department of Health and Human Services goal. The aim of this work was to assess the vaccination rate among patients who present to health care providers with influenza-like illness and identify groups with lower vaccination rates.

**Methods.** We performed a systematic search of the PubMed and EMBASE databases with a time frame of January 1, 2010, to March 1, 2019 and focused on the vaccination rate among patients seeking care for acute respiratory illness in the United States. A random effects meta-analysis was performed to estimate the pooled seasonal influenza vaccination rate, and we used a time trend analysis to identify differences in annual vaccination over time.

**Results.** The overall pooled influenza vaccination rate was 48.61% (whites: 50.87%; blacks: 36.05%; Hispanics: 41.45%). There was no significant difference among gender groups (men: 46.43%; women: 50.11%). Interestingly, the vaccination rate varied by age group and was significantly higher among adults aged >65 (78.04%) and significantly lower among children 9–17 years old (36.45%). Finally, we found a significant upward time trend in the overall influenza vaccination rate among whites (coef. = .0107;  $P = .027$ ).

**Conclusions.** In conclusion, because of the significantly lower influenza vaccination rates in black and Hispanic communities, societal initiatives and community outreach programs should focus on these populations and on children and adolescents aged 9–17 years.

**Keywords.** acute respiratory illness; influenza; meta-analysis; systematic review; vaccination.

Influenza infections are a major cause of morbidity and mortality. The Centers for Disease Control and Prevention (CDC) has estimated that during the 2017–2018 season, there were 48.8 million influenza infections that resulted in 22.7 million ambulatory health care visits, 959 000 hospitalizations, and 79 400 deaths [1]. Vaccination is widely considered to be the most cost-effective strategy against influenza infection [2]. Following the influenza A(H1N1)pdm09 pandemic, the CDC Advisory Committee on Immunization Practices (ACIP) expanded the existing guidelines and recommended universal annual vaccination in adults and children older than 6 months of age [3]. The CDC estimates that in the 2017–2018 season in the United

States, the vaccination rate was 37.1% for adults [4] and 57.9% for children 6 months to 18 years old [5]. However, vaccination rates have remained significantly lower than the Department of Health and Human Services goal, which has been set at 80% for healthy adults and 90% for high-risk adults and elderly individuals [6].

Given the expanded recommendations, population-wide assessments of vaccination rate and effectiveness have become important [7]. To estimate the vaccination rate for the US population, the CDC analyzes data from the Behavioral Risk Factor Surveillance System (BRFSS), a state-based program that uses telephone surveys to collect information on health conditions of randomly selected individuals [8]. Estimates following the influenza A(H1N1)pdm09 pandemic ranged from a nadir of 37.1% in 2017–2018 to a peak of 43.6% in 2014–2015 [4]. Although this approach is likely to give an accurate estimate of the vaccination rate of the total US population, it might be less sensitive in reflecting the compliance of individuals in contact with the health care system [9]. Moreover, patients with comorbidities are at high risk for complications and are more likely to seek health care during a respiratory illness, making this population of

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particular interest regarding influenza vaccine uptake [10]. In this systematic review, we aim to assess the vaccination rate among patients who present to health care providers with influenza-like illness and identify subgroups with lower vaccination rates.

## METHODS

We performed a systematic search of the PubMed and EMBASE databases from the implementation of the 2010 guidelines to March 1, 2019, to identify all studies reporting influenza vaccination status among patients seeking care for acute respiratory illness. We used the following search terms: (influenza OR flu) AND (vaccine OR vaccination) AND (respiratory illness OR respiratory infection). Titles and abstracts were screened independently by 2 authors (M.K., F.S.), and all relevant studies were accessed in full text. References of the studies that were eligible for inclusion were also reviewed. As vaccination data and guidelines vary, only data from the United States were analyzed. This systematic review and meta-analysis was conducted according to the Meta-analysis of Observational Studies in Epidemiology (MOOSE) guidelines (Supplementary Table 1) [11].

### Study Selection and Outcomes of Interest

Studies were considered eligible and included in our study if they reported extractable data on the rate of influenza vaccination among patients with medically attended acute respiratory illness in the United States starting in the 2011–2012 season. Studies that did not provide data on influenza vaccination, grouped by race, gender, and age, and studies reporting only summary data from multiple influenza seasons were excluded. The primary outcome of interest was the cumulative annual influenza vaccination rate of patients seeking care for acute respiratory illness. Subgroup estimates for age, gender, and race were examined. As a secondary outcome of interest, we performed a time trend analysis to identify differences in annual vaccination over time.

### Data Extraction and Quality Assessment

Two authors (M.K. and F.S.) independently screened and evaluated eligible articles. Data from the eligible studies were extracted by F.S. and T.K. Discrepancies were resolved by a third reviewer (M.K.) and consensus. The following information was extracted from each included study: influenza season, total number of vaccinated and unvaccinated subjects, number of vaccinated and unvaccinated subjects per race, number of vaccinated and unvaccinated subjects per gender, and number of vaccinated and unvaccinated subjects per age group.

The quality of the eligible studies was assessed independently by 2 reviewers (F.S., M.K.) using the National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies [12].

### Data Synthesis and Analysis

We performed a random effects meta-analysis to estimate the pooled seasonal influenza vaccination rates, grouped by gender, age, and race, and their 95% confidence intervals using the DerSimonian and Laird approach [13]. The Freeman Tukey double arcsine transformation was utilized to stabilize the variances [14]. A random effects approach was chosen because we assumed that the effects were heterogeneous due to differences in the study settings and the parameters affecting vaccination each year. Heterogeneity between studies and subgroups was assessed using the  $I^2$  statistic [14], and the Egger's test was used to check for publication bias and small study effects.

A metaregression analysis was performed to model time trends using the first year of each influenza season as a continuous variable. Plots with prediction confidence intervals were produced to display and interpret the results of the time trend analysis. Stata, version 15.1 (Stata Corporation, College Station, TX, USA), was used for the statistical analysis. The significance threshold was set at .05.

## RESULTS

Our systematic search yielded 1716 nonduplicate citations to evaluate. After title and abstract screening, 57 studies were identified as eligible for full-text review. Of these studies, 9 fulfilled our inclusion criteria and were included in our meta-analysis (Table 1). The detailed review process is shown in Supplementary Figure 1. The included studies provided data from 46 462 patients and included data from the 2011–2012 through the 2018–2019 flu seasons, published from 2014 to 2019.

All included studies were prospective and multicenter. Eight studies included data from the US Flu Vaccine Effectiveness Network sites in MI, PA, TX, WA, WI [7, 15–17, 19, 21, 22]. One study included data from sites in NC, TN, TX, WI [18]. All the studies included visits to outpatient clinics only. Patients were enrolled if they presented with acute respiratory illness and cough in 7 studies [15–17, 19, 21, 22], acute respiratory illness and fever in 1 study [18], and acute respiratory illness and cough or fever in 1 study [7]. Vaccination status was ascertained from medical records, vaccine registries, and self-report (Table 1). No study was excluded due to quality concerns.

The proportion of vaccinated subjects seeking care for acute respiratory illness varied from 44.59% to 54.98% (Figure 1), and the overall pooled influenza vaccination rate was 48.61% (95% CI, 46.66%–50.56%). Egger's test for publication bias detected no evidence of small-study effects (bias, 5.72;  $P = .413$ ). The  $I^2$  statistic found considerable heterogeneity between the studies ( $I^2 = 94.3\%$ ;  $P < .001$ ). When subgrouped by race, the vaccination rate was significantly higher for whites (50.87%;

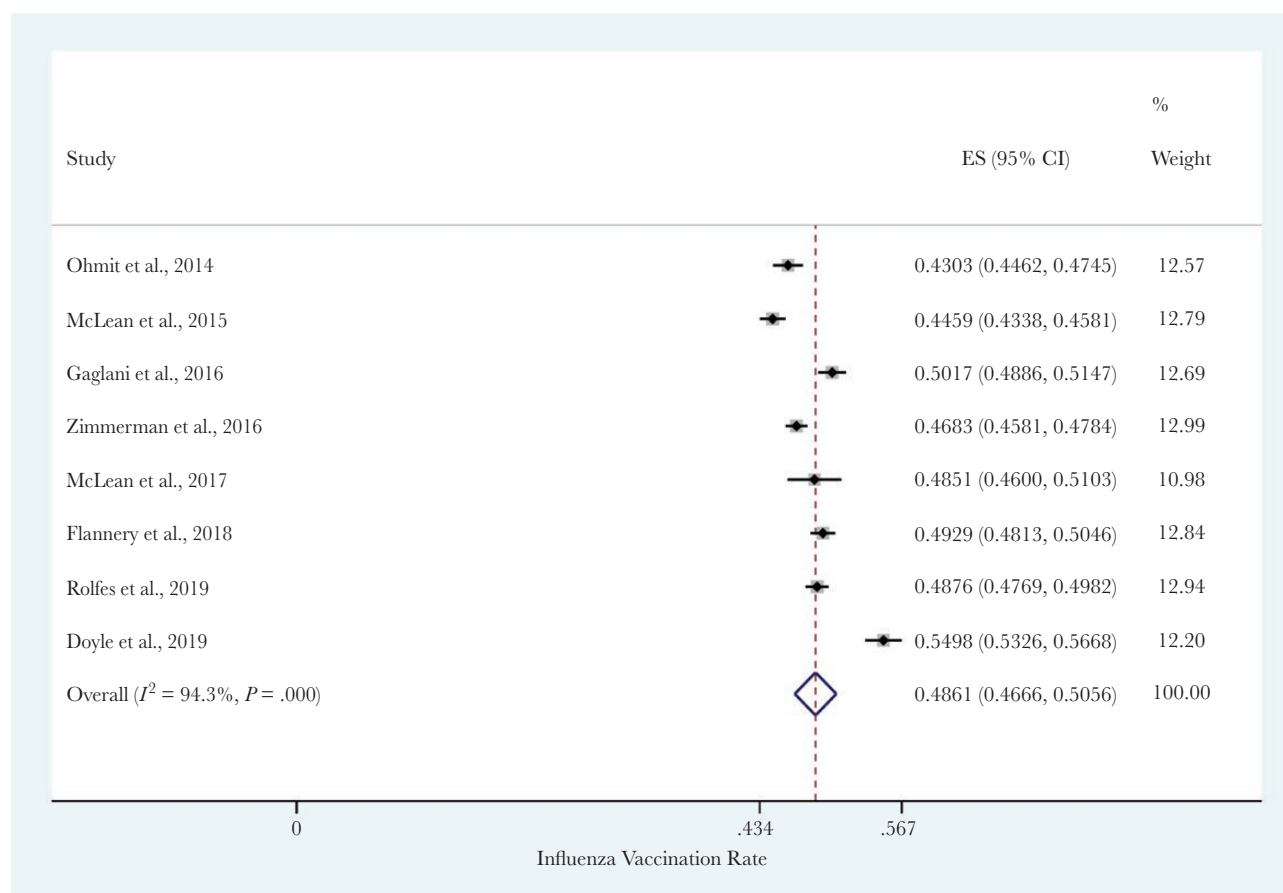
**Table 1. Study Characteristics**

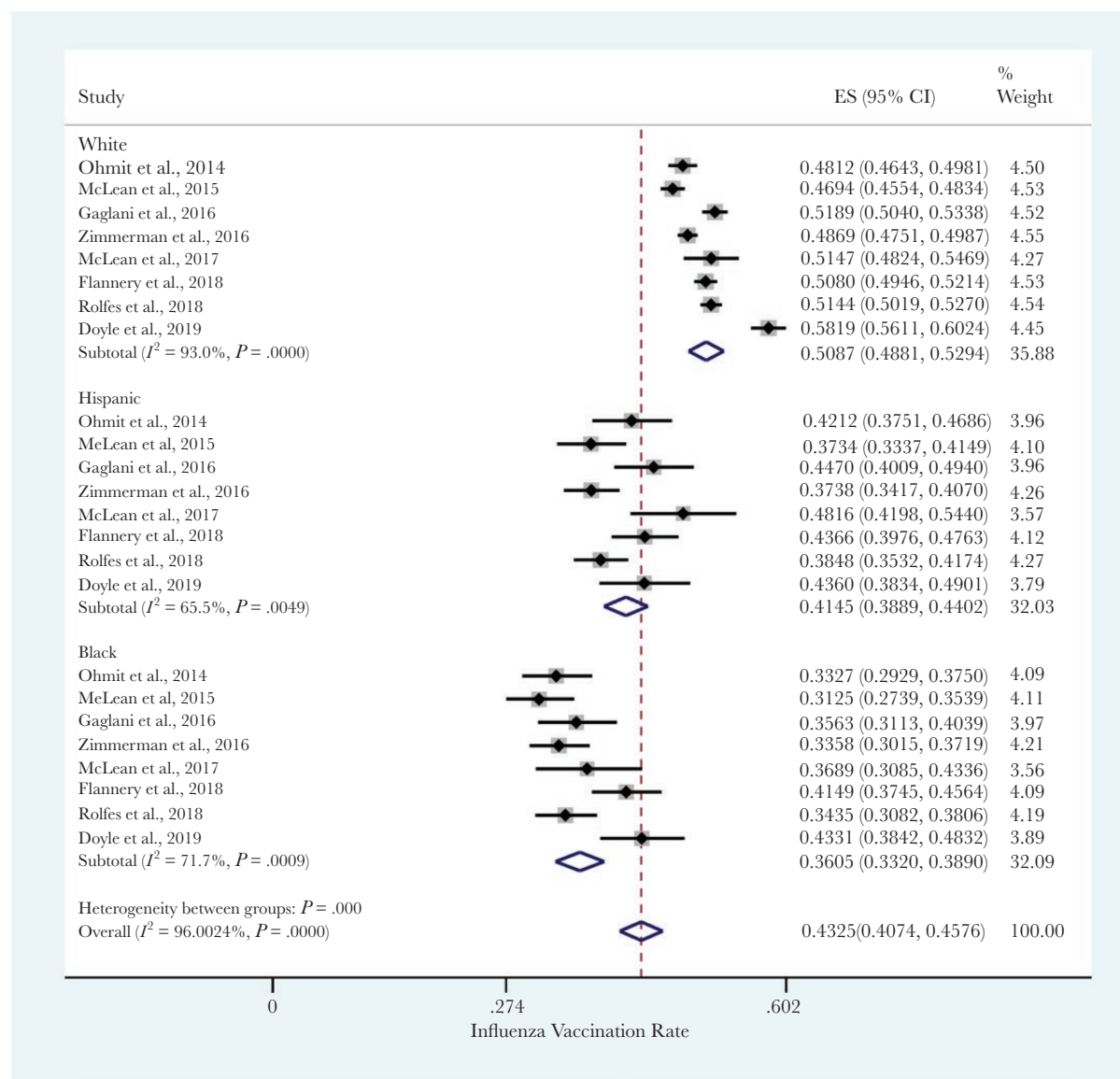
Study	Season	Subjects, No.	Age, Male, %	Setting	Vaccination Documentation	ARI Definition	States
McLean et al., 2015 [15]	2012–2013	6452	≥6 mo, 41%	Outpatient clinics	MR, VR, SR	ARI and cough	MI, PA, TX, WA, WI
Ohmit et al., 2014 [7]	2011–2012	4771	≥6 mo, 51%	Outpatient clinics	MR, VR	ARI and cough or fever	MI, PA, TX, WA, WI
Gaglani et al., 2016 [16]	2013–2014	5637	≥6 mo, 42%	Outpatient clinics	MR, VR, SR	ARI and cough	MI, PA, TX, WA, WI
Zimmerman et al., 2016 [17]	2014–2015	9311	≥6 mo, 42%	Outpatient clinics	MR, VR, SR	ARI and cough	MI, PA, TX, WA, WI
McLean et al., 2017 [18]	2014–2015	1511	2–17 y, 50%	Outpatient clinics	MR, VR	ARI and fever	NC, TN, TX, WI
Flannery et al., 2018 [19]	2017–2018 interim	4562	≥6 mo, 41%	Outpatient clinics	MR, VR, SR	ARI and cough	MI, PA, TX, WA, WI
Rolfes et al., 2019 [20]	2017–2018	8436	≥6 mo, 41%	Outpatient clinics	MR, VR, SR	ARI and cough	MI, PA, TX, WA, WI
Flannery et al., 2018 [21]	2016–2017	7083	≥6 mo, 42%	Outpatient clinics	MR, VR, SR	ARI and cough	MI, PA, TX, WA, WI
Doyle et al., 2019 [22]	2018–2019	3254	≥6 mo, 41%	Outpatient clinics	MR, VR, SR	ARI and cough	MI, PA, TX, WA, WI

Abbreviations: ARI, acute respiratory illness; MR, medical records; SR, self-report; VR, vaccine registries.

95% CI, 48.81%–52.94%), compared with blacks (36.05%; 95% CI, 33.20%–38.90%) and Hispanics (41.45%; 95% CI, 38.89%–44.02%) (Figure 2).

Subgrouped by gender, the influenza vaccination rate pooled estimate varied, but the difference did not reach statistical significance and was 46.43% (95% CI, 44.37%–48.50%) for men

**Figure 1.** Forest plot of included studies.



**Figure 2.** Forest plot of included studies stratified by race.

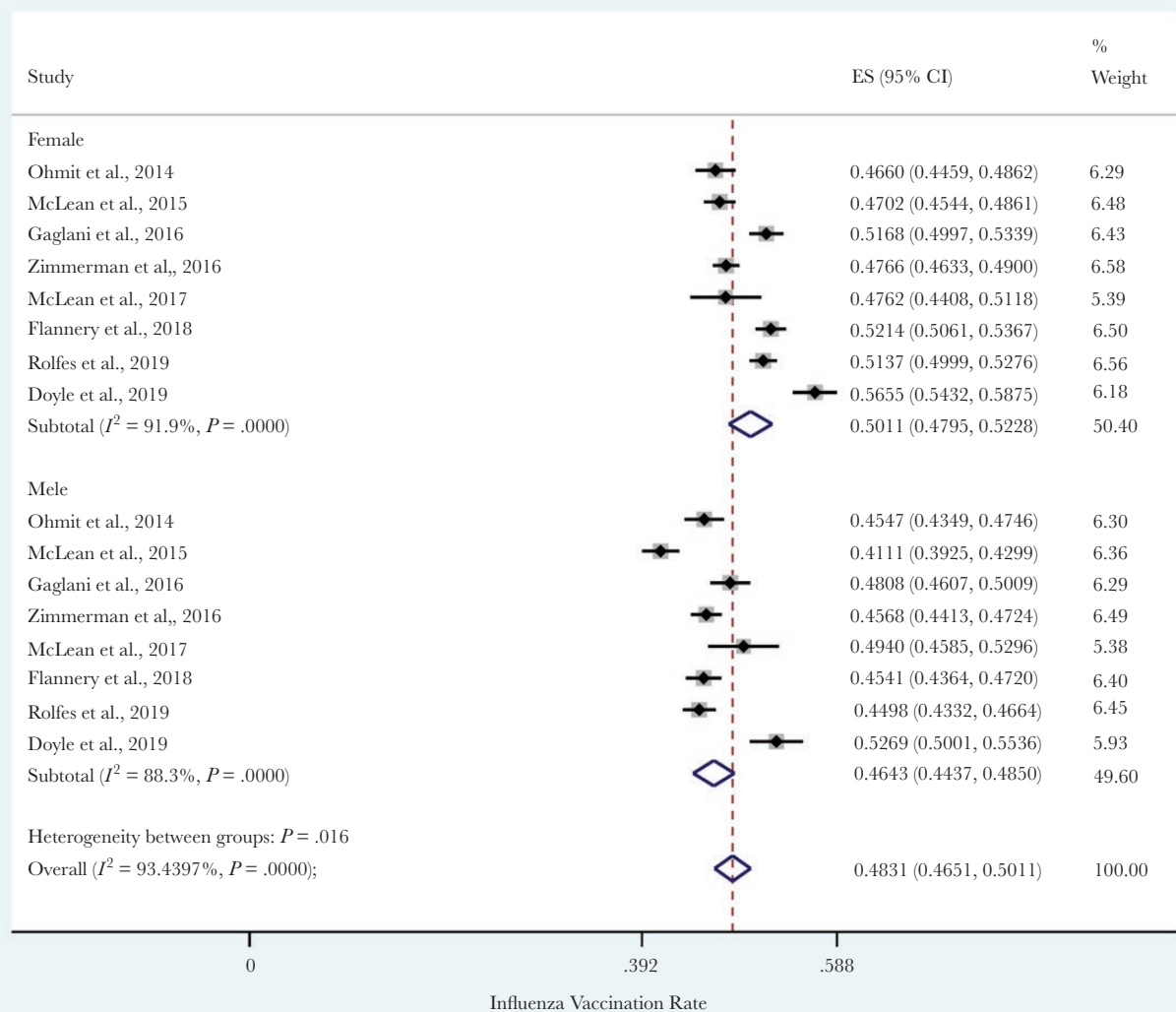
and 50.11% (95% CI, 47.95%–52.28%) for women (Figure 3). When subgrouped by age, the vaccination rate varied by age group and was significantly higher in the elderly population and significantly lower in children 9 to 17 years old, compared with adults 18 to 64 years old and children 6 months to 8 years old (Figure 4). In particular, the influenza vaccination rate was 49.48% (95% CI, 46.52%–52.44%) for children 6 months to 8 years old, 36.45% (95% CI, 34.54%–38.35%) for children and adolescents 9 to 17 years old, 44.30% (95% CI, 41.83%–46.76%) for adults 18 to 64 years old, and 78.04% (95% CI, 75.63%–80.45%) for adults older than 65.

A metaregression analysis was performed to evaluate the time trend of influenza vaccination rate, yielding a significant upward trend in the overall influenza vaccination rate (coef. = .0097;  $P = .030$ ), as shown in Figure 5A. When subgrouping for race,

the vaccination rate of white populations followed a significant upward trend (coef. = .0107;  $P = .027$ ) and a slight upward trend for black populations that did not reach significance (coef. = .0120;  $P = .057$ ), while remaining significantly different for all flu seasons throughout the years studied (Figure 5B). The time trend analysis of the vaccination rate of Hispanics did not show a significant trend ( $P = .853$ ).

When subgrouping by gender, time trend analysis yielded a significant upward trend for vaccination of women (coef. = .0113;  $P = .013$ ) but did not show a significant trend for men ( $P = .210$ ), and the trends were not statistically different, as evidenced by the overlap between their confidence intervals for all the flu seasons studied (Figure 5C).

Finally, when subgrouping by age (Figure 5D), time trend analysis yielded a slight upward trend for the 4 age groups



**Figure 3.** Forest plot of included studies stratified by gender.

examined. The trend was significant for adults 18 to 64 years old (coef. = .0107;  $P = .034$ ) but did not reach statistical significance for children 6 months to 8 years old (coef. = .0024;  $P = .749$ ), children and adolescents 9 to 17 years old (coef. = .0039;  $P = .429$ ), or adults older than 65 (coef. = .0999;  $P = .71$ ).

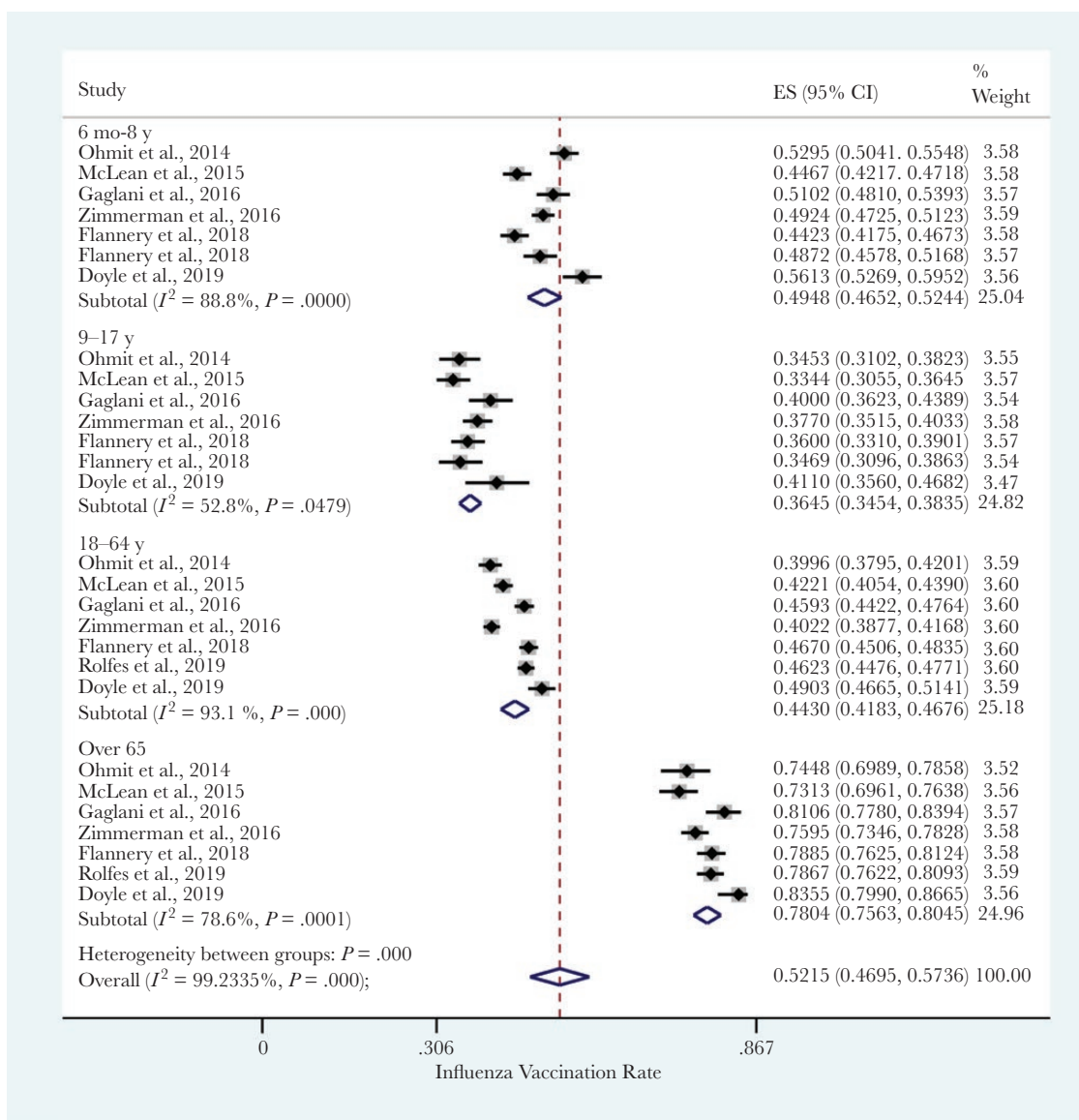
## DISCUSSION

We systematically assessed the vaccination rate among individuals who presented to an outpatient clinic seeking medical care for acute respiratory illness after the expanded recommendations for universal immunization in adults and children older than 6 months of age. We found a low cumulative vaccination rate of 48.61% among medically attended patients with acute respiratory illness. Although a significant upward trend over time was observed for white populations, there was no time trend observed for black or Hispanic populations and

vaccination coverage remained low. Furthermore, there were significant differences among demographic groups, with a significantly higher vaccination rate in elderly patients aged >65, compared with children and young adults, as well as among white individuals compared with blacks and Hispanics.

The cumulative vaccination rate of almost 50% that we found among all patients who presented for an ambulatory health care visit for acute respiratory illness on or after the 2011–2012 season is higher than the CDC overall estimates for the same time period, which range from a nadir of 37.1% in 2017–2018 [4] to a peak of 43.6% in 2014–2015 [23]. The observed higher vaccination compliance among the patient subgroup that presented for evaluation to the health care system could be secondary to the overrepresentation of patients who were at higher risk of developing influenza-related complications in our analysis [10]. Differences in sampling methods could also have contributed to the higher vaccination rate observed in our analysis.



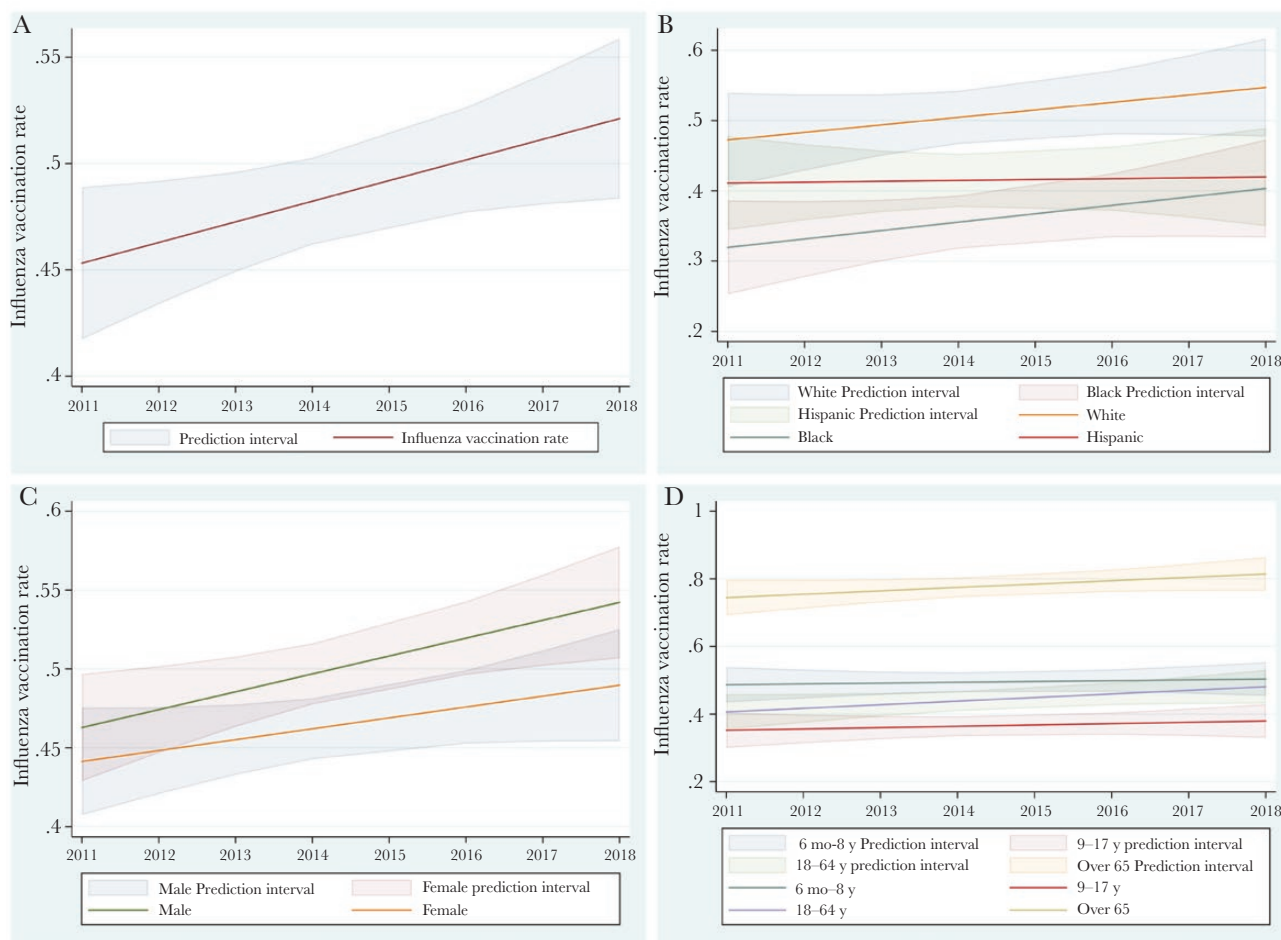


**Figure 4.** Forest plot of included studies stratified by age.

The CDC analyzes data from the Behavioral Risk Factor Surveillance System, which is a state-based telephone survey that has been collecting information on health conditions and risk behaviors since 1984 [8]. As response to the telephone surveys is voluntary, selection bias may have been introduced from a high nonresponse rate in BRFSS surveys, which was >50% for the 2017–2018 season [24]. Indeed, a study that compared the BRFSS national estimates to the National Health Interview Survey (NHIS), which is conducted by the National Center for Health Statistics of the Centers for Disease Control and Prevention through a personal household interview, showed that BRFSS estimates for influenza immunization were 2.3% lower than the NHIS estimates [25]. Also, unlike studies included in the present analysis, the majority of which verified self-reporting of influenza vaccination status with medical

record data, BRFSS vaccination rates are based on patient recall. Studies have estimated that while the sensitivity of self-reporting is high, there is low specificity [26] and therefore BRFSS data might underestimate the influenza vaccination rate.

Unlike CDC estimates that the influenza vaccination rate has remained stable over the last 10 years, we detected a significant upward trend over time. This could again be secondary to the facts that the patient population of our study is more likely to have come in contact with the health care system and the intensified efforts to increase vaccination compliance in this patient subgroup over time. On the other hand, based on the NHIS survey in 2017, almost 40% of adults aged 18–44 years reported that they had not had contact with a health care provider in the last  $\geq 6$  months [27]. More importantly, based on a Kaiser Family Foundation analysis of the BRFSS 2015–2017 Survey



**Figure 5.** Time trend analysis of the influenza vaccination rate (A) overall, (B) stratified by race, (C) stratified by gender, and (D) stratified by age.

Results, 28% of men and 17% of women do not have a primary care provider [28]. Taken together with the absence of societal initiatives and community outreach to increase vaccine uptake [29], surveys on the vaccination compliance of the general population might not be able to detect coverage increases in high-risk patient subgroups.

Despite the upward trend in our analysis, vaccination rates remain low overall. Identifying specific factors that play a role in an individual's decision to receive vaccination is an important step toward tailored interventions. Two previous literature reviews that included >500 studies examined the potential factors behind vaccine hesitancy and found that factors such as low disease risk perception, high perceived risk of vaccine side effects, negative past experience, personal attitudes, lack of knowledge, and perceived behavioral control may negatively impact influenza vaccine uptake among individuals [30, 31]. Furthermore, vaccine uptake has been associated with socioeconomic factors and education level [32]. In general, the reasons behind vaccine hesitancy can be summarized by the 4C model: Complacency, lack of Convenience, lack of Confidence, and Calculation (ie, vaccination risks outweigh potential benefits) [33]. On the

other hand, the feeling of social benefit, a history of previous vaccination, the presence of social pressure, a direct recommendation from medical personnel, and interaction with the health care system may play a positive role toward vaccine uptake [31]. Finally, although the impact of the few existing strategies to address vaccine hesitancy is not well established to date, strategies that have multiple components, are dialogue-based, and address specific patients' concerns or doubts tend to perform better [31, 34].

In agreement with BRFSS data [4] and data from Medicare beneficiaries [35], we observed racial disparities, with whites having a higher vaccination rate than Hispanics and blacks. The above observation is likely multifactorial and might be partially explained by differences in socioeconomic status and access to care [35, 36]. In addition, ethnic minorities might be more prone to missing opportunities to vaccinate during medical visits [37]. Of note, while we observed an increase in vaccination rate among white populations, it is worrisome that the vaccination rate among black and Hispanic populations has remained relatively stable and low. Interestingly, when Chen et al. [38] examined the main barriers to vaccination among different



ethnic groups, they found that Hispanics were more likely to report access and cost as vaccination barriers, while black individuals were more likely to raise issues of mistrust against influenza vaccine. In this regard, public policies should be tailored to address specific minority barriers, and future studies should examine initiatives to increase vaccine uptake in these populations.

The limitations of this study include that the published studies are not representative of the entire US population and some states are not represented in the studies included in our analysis, while certain medical sites are overrepresented. Furthermore, data on some of the subgroups were missing in some studies, while there were sites in the included studies that did not verify immunization status by medical records.

## CONCLUSIONS

We examined the vaccination rate among individuals who sought care for acute respiratory illness in the United States, and almost half were vaccinated. While significantly lower than the goal of 80% to 90% for 2020, the calculated vaccination rate was higher and with an increasing trend, compared with that reported by nationwide surveys. However, racial and age disparities were detected, with lower influenza vaccination rates among black and Hispanic populations and among children and adolescents aged 9–17 years. The analysis identifies subgroups with lower immunization compliance that should be targeted by societal initiatives and community outreach programs.

## Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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**Potential conflicts of interest.** Dr. Mylonakis has received grant support from T2 Biosystems, Sanofi-Aventis, Kaleido Biosciences, and Cidara Therapeutics. Mr. van Aalst and Dr. Chit report having been employees of Sanofi-Pasteur during the conduct of the study. The rest of the authors have disclosed no conflicts of interest. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

**Author contributions.** F.S., I.M.Z., M.K., E.K.M., T.K., R.v.A., A.C., and E.M. contributed to the study concept and design. F.S., M.K., and T.K. performed the literature search and data extraction. F.S. and E.K.M. performed the statistical analysis. All authors were involved in data analysis or review and manuscript preparation. F.S. is the guarantor and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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